Role of Serotonin in Patients with Acute Respiratory Failure

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An early event in the evolution of acute respiratory failure (ARF) is thought to be the activation of platelets, their pulmonary entrapment and subsequent release of the smooth muscle constrictor serotonin (5HT). This study tests the thesis that inhibition of 5HT will improve lung function. The etiology of ARF in the 18 study patients was sepsis (N = 10), aspiration (N = 3), pancreatitis (N = 1), embolism (N = 2), and abdominal aortic aneurysm surgery (N = 2). Patients were divided into two groups determined by whether their period of endotracheal intubation was less than or equal to 4 days (early ARF, N = 12) or greater than 4 days (late ARF, N = 6). Transpulmonary platelet counts in the early group showed entrapment of 26,300 ± 5900 platelets/mm^3 in contrast to the late group where there was no entrapment ($p < 0.05$). The platelet 5HT levels in the early group were 55 ± 5 ng/10^9 platelets, values lower than 95 ± 15 ng/10^9 platelets in the late ARF group ($p < 0.05$), and 290 ± 70 ng/10^9 platelets in normals. The selective 5HT receptor antagonist, ketanserin was given as an intravenous bolus over 3 minutes in a dose of 0.1 mg/kg, followed by a 30-minute infusion of 0.08 mg/kg. During this period mean arterial pressure (MAP) fell from 87 ± 5 to 74 ± 6 mmHg (mean ± SEM) ($p < 0.05$). One and one-half hours following the start of therapy, MAP returned to baseline. At this time, patients with early ARF showed decreases in: physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) from 26 ± 3 to 19 ± 3 ($p < 0.05$); peak inspiratory pressure from 35 ± 2 to 32 ± 2 cmH_2O ($p < 0.05$) and in mean pulmonary arterial pressure from 32 ± 2 to 29 ± 1 mmHg ($p < 0.05$). At 4 hours all changes returned to baseline levels. In early ARF ketanserin did not alter pretreatment values of: pulmonary arterial wedge pressure, 17 ± 3 mmHg; cardiac index, 2.8 ± 0.3 L/min · m^2; platelet count, 219,000 ± 45,000/mm^3; platelet 5HT, 55 ± 5 ng/10^9 platelets; plasma 5HT, 142 ± 21 ng/ml; plasma thromboxane B_2, 190 ± 30 pg/ml; or plasma 6-keto-$PGF_{1\alpha}$, 40 ± 10 pg/ml. Ketanserin infusion in patients with late ARF yielded no benefit. In both ARF groups the decreases in $\dot{Q}_S/\dot{Q}_T$ were inversely related to the duration of intubation ($r = 0.70$; $p < 0.05$). The data indicate that platelet entrapment and 5HT released in the first 4 days of ARF results in significant impairment of lung function by constriction of the pulmonary vasculature and bronchi.

PULMONARY ARTERY HYPERTENSION frequently accompanies the hypoxia of acute respiratory failure (ARF). Platelets and leukocytes are thought to be paramount in the etiology of these lung abnormalities.[1-3] In a previous study it was shown that both cell types are entrapped in the lungs of patients with ARF.[1] Platelets are believed to be of particular importance in early vaso- and bronchospastic events because of their ability to release serotonin. Serotonin (5HT) is a smooth muscle constrictor released by activated platelets, which may mediate in part the pulmonary hypertension and hypoxia of ARF.[4-6] Normally, 70% to 90% of this amine is actively removed from the circulation by pulmonary endothelial cells during a single passage through the lung.[7] Local platelet release of 5HT in the lungs combined with a possible defect in endothelial 5HT transport and metabolic deactivation could lead to pulmonary dysfunction. This study tests the thesis that platelet entrapment in the lungs with release of 5HT contributes to the early pulmonary functional abnormalities of ARF.

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Materials and Methods

The current study was performed on 18 patients who were admitted to the Surgical Intensive Care Unit of the Brigham and Women's Hospital from January 2, 1982 through April 8, 1983 with the diagnosis of ARF. This diagnosis was based on the need for endotracheal intubation, mechanical ventilatory support, and supplementary oxygen. The patients' mean ages were 65 ± 4 years (mean ± standard error), and weight 75 ± 5 kg. The etiologies of ARF were: sepsis (N = 10), gastric aspiration (N = 3), pancreatitis (N = 1), pulmonary embolus (N = 2), and abdominal aortic aneurysm surgery (N = 2).

Only patients who were intubated, requiring mechanical ventilation, as well as pulmonary artery catheterization for support were considered for admission into this study. In addition, patients who were accepted into the study had a physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) greater than 20%, and a mean pulmonary artery pressure exceeding 25 mmHg. Patients were then divided into groups based on

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TABLE 1. *Patient Profile*

Age/Sex	Wt (kg)	Diagnosis	Days* SICU	Days* Intub	Pulmonary edema (x-ray)	History of Smoking	History of COPD†	Per cent Inspired O_2
				Early				
88/F	52	Intra-abdominal abscess	2	2	+	−	−	50
51/M	68	Intra-abdominal abscess	4	4	+	+	+	80
73/F	60	Pulmonary embolism	1	1	−	−	−	80
71/M	89	Pancreatitis	3	3	−	−	−	80
52/F	75	Retroperitoneal abscess	1	1	+	+	−	80
71/F	93	Intra-abdominal abscess	5	4	+	?	−	50
78/M	78	Ruptured abdominal aortic aneurysm	2	2	+	+	+	100
81/F	51	Aspiration	1	1	+	−	−	40
74/F	60	Intra-abdominal abscess	1	1	+	−	−	40
72/M	79	Abdominal aortic aneurysm repair	2	2	−	+	−	40
35/F	60	Mediastinitis	1	1	+	+	−	60
84/M	95	Aspiration	2	2	+	+	+	50
69 ± 4	72 ± 4		2 ± 1	2 ± 1				62 ± 10
				Late				
59/F	120	Intra-abdominal abscess	5	5	−	+	+	100
50/F	52	Intra-abdominal abscess	10	6	+	+	−	60
39/M	93	Burn	19	6	+	−	−	60
80/M	81	Aspiration	5	5	+	+	−	70
63/F	93	Pulmonary embolism	14	10	−	+	−	40
60/F	47	Mediastinitis	12	12	+	+	+	50
60 ± 6	81 ± 9		11 ± 2	7 ± 2				62 ± 8

* Days in the Surgical Intensive Care Unit (SICU) or intubated (Intub). The presence of pulmonary edema on chest x-ray, as well as a prior history of smoking or chronic obstructive pulmonary disease (COPD),† is indicated as +.

the number of days intubated. Patients intubated 4 days or less were designated as "early" ARF (N = 12), while those intubated longer than 4 days were assigned to the "late" ARF group (N = 6). The profile of patients admitted to the early and late groups were similar (Table 1).

After baseline measurements and blood samples were obtained, ketanserin, a relatively selective 5HT receptor antagonist,[8,9] was administered intravenously in a bolus of 0.1 mg/kg over 3 minutes, followed by an infusion of 0.08 mg/kg over 30 minutes. Measurements of interest were again obtained at 5 minutes, 1 hour, and 4 hours after infusion. During this period tidal volume was kept constant.

Strain gauge transducers were used to measure mean arterial (MAP), mean pulmonary arterial (MPAP), central venous (CVP) and pulmonary arterial wedge (PAWP) pressures. Cardiac output was determined in triplicate by thermodilution (Instrumentation Laboratory, model 601) and divided by body surface area to obtain cardiac index (CI). Blood gases, pH, and saturation of arterial and mixed venous blood were measured using Clark and Severinghaus electrodes, and spectrophotometry (Instrumentation Laboratory, models 813 and 282). Physiologic shunt, the percentage of flow exiting the lungs with the same oxygen content as pulmonary arterial blood, was calculated from the Berggren equation[10] using the following formula:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_{\bar{v}}O_2} \times 100$$

where C_cO_2, C_aO_2, $C_{\bar{v}}O_2$ are oxygen contents in capillary, arterial, and mixed venous or pulmonary arterial blood, respectively.

Platelets were counted in arterial and mixed venous blood using phase microscopy. Washed platelets and plasma were prepared from blood collected in ethylenediamine tetraacetic acid (EDTA) (1% EDTA in 0.9% saline, 1:9) according to the method of Zucker.[11] Plasma and platelet 5HT were fluorophotometrically determined by the formation of a fluorophore with O-phthaldialdehyde (Sigma Chemical). Blanks were prepared by adding 10 μl of 0.2% potassium ferricyanide (Fisher Scientific) to each assay tube. Fluorescence was measured using a spectrofluorometer (Perkin-Elmer, model MPF-44B) with excitation and emission wavelengths of 360 and 475 nm, respectively. Plasma thromboxane (Tx) B_2 and 6-keto-$PGF_{1\alpha}$, the stable degradation products of TxA_2 and prostacyclin, respectively, were measured by radioimmunoassay,[12] as previously described.[13]

TABLE 2. *Ketanserin Therapy of Acute Respiratory Failure*

		Baseline	Hours Postinfusion 0.5	1.0	4.0
		Early			
Heart rate (HR)	(beats/min)	109 ± 5	109 ± 6	110 ± 5	106 ± 5
Pulmonary arteral wedge pressure (PAWP)	(mmHg)	17 ± 2	15 ± 2	16 ± 2	16 ± 2
Centralvenous pressure (CVP)	(mmHg)	14 ± 1	13 ± 2	13 ± 2	14 ± 1
Cardiac index (CI)	($L/min \cdot m^2$)	2.8 ± 0.3	2.9 ± 0.3	2.9 ± 0.4	2.9 ± 0.3
Platelets	($\cdot 10^3 \cdot mm^{-3}$)	220 ± 44	157 ± 30	203 ± 53	196 ± 41
WBC	($\cdot 10^3 \cdot mm^{-3}$)	12.3 ± 1	12.5 ± 3.1	11.9 ± 2	10.2 ± 2.8
Platelet 5HT	($ng/10^9$ plt)	55 ± 5	73 ± 7	58 ± 6	48 ± 5
Plasma 5HT	(ng/ml)	142 ± 21	148 ± 20	163 ± 51	174 ± 18
Plasma thromboxane (TxB_2)	(pg/ml)	190 ± 30	200 ± 50	210 ± 80	180 ± 50
6-keto-$PGF_{1\alpha}$	(pg/ml)	40 ± 10	50 ± 10	60 ± 10	40 ± 10
		Late			
HR	(beats/min)	113 ± 5	111 ± 4	111 ± 4	114 ± 5
PAWP	(mmHg)	14 ± 1	13 ± 1	14 ± 1	14 ± 1
CVP	(mmHg)	14 ± 1	13 ± 2	14 ± 2	12 ± 2
CI	($L/min \cdot m^2$)	3.3 ± 0.5	3.1 ± 0.4	3.0 ± 0.4	3.2 ± 0.4
Plt	($\cdot 10^3 \cdot mm^{-3}$)	201 ± 46	158 ± 50	178 ± 51	204 ± 25
WBC	($\cdot 10^3 \cdot mm^{-3}$)	12.6 ± 1.7	12.2 ± 3.2	10.7 ± 2.3	11.6 ± 3.6
Platelet 5HT	($ng/10^9$ plt)	95 ± 15	108 ± 12	110 ± 18	130 ± 18
Plasma 5HT	(ng/ml)	146 ± 23	170 ± 35	159 ± 26	155 ± 27
TxB_2	(pg/ml)	250 ± 40	250 ± 40	220 ± 40	260 ± 40
6-keto-$PGF_{1\alpha}$	(pg/ml)	40 ± 10	40 ± 10	30 ± 10	40 ± 10

All data in the tables, figures, and text are presented as mean ± standard error. Statistics were performed using paired and nonpaired Student's t-tests where applicable. A p value < 0.05 was accepted as significant.

Investigations involving human subjects were conducted in conformity with the principles embodied in the Helsinki Declaration of 1975; and were approved by the Brigham and Women's Hospital and Harvard Medical School Institutional Review Boards for Human Research. Informed consent was obtained for each subject.

Results

Patients studied early or late in the course of their ARF had similar profiles (Table 1), as well as hemodynamic and hematologic measurements (Table 2). Baseline plasma TxB_2 levels in early and late ARF patients were 190 ± 30 pg/ml and 250 ± 40 pg/ml, respectively, while 6-keto-$PGF_{1\alpha}$ levels were 40 ± 10 pg/ml in both groups (Table 2). In normal volunteers, TxB_2 and 6-keto-$PGF_{1\alpha}$ have been found to be 60 ± 10 pg/ml and 20 ± 10 pg/ml, respectively.

Differences were noted in pulmonary platelet entrapment and evidence of 5HT release. In the early ARF group, platelet counts in pulmonary arterial blood were 26,300 ± 5900 platelets/cm^3 higher than arterial counts. This differed significantly from the pulmonary minus arterial platelet counts of −12,400 ± 9100 platelets/cm^3 for the late ARF patients ($p < 0.05$). In the early ARF group, platelet 5HT levels were 55 ± 5 $ng/10^9$ platelets, values that were lower than 95 ± 15 $ng/10^9$ platelets noted in the late ARF group ($p < 0.05$) and lower than 290 ± 70 $ng/10^9$ platelets found in normals.

Within 15 minutes, infusion of ketanserin led to a decline in MAP from 90 ± 7 to 72 ± 7 mmHg in the early ARF group ($p < 0.05$) and from 85 ± 5 to 77 ± 6 mmHg in the late group ($p < 0.05$) (Fig. 1). One and one-half hours following the start of therapy, MAP had returned to baseline in both groups. At this time in early ARF patients, MPAP was 29 ± 1 mmHg, a value lower than the baseline level of 32 ± 2 ($p < 0.05$) (Fig. 2); $\dot{Q}_S/\dot{Q}_T$ had decreased from a baseline of 26 ± 3 to 19 ± 3% ($p < 0.05$), and PaO_2 rose from 91 ± 7 to 103 ± 7 mmHg ($p < 0.05$) (Fig. 3). Further, at 1.5 hours, the peak inspiratory pressure for the early group was 32 ± 2 cm H_2O, a value lower than the baseline level of 35 ± 2 ($p < 0.05$) (Fig. 4). At 4 hours, all measurements had returned to baseline levels. In the late ARF group, ketanserin therapy had no effect on MPAP, $\dot{Q}_S/\dot{Q}_T$, or peak inspiratory pressure. When all study patients were considered, the decrease in $\dot{Q}_S/\dot{Q}_T$ in response to ketanserin treatment was inversely related to the duration of intubation ($r = 0.70$) ($p < 0.05$) (Fig. 5). The effect of ketanserin administration on $\dot{Q}_S/\dot{Q}_T$ was greatest when given early in the course of ARF. A septic patient treated 2 hours after intubation had a decline in $\dot{Q}_S/\dot{Q}_T$ from 48% to 28% (Fig. 6).

In neither group did ketanserin infusion significantly alter heart rate, PAWP, or CI (Table 2). Further, this 5HT receptor antagonist had no influence on plasma or platelet 5HT levels or platelet counts. Plasma prostanoid concentrations were constant throughout the 4-hour study period (Table 2).

Discussion

The current study indicates that platelet entrapment in the lungs and 5HT release is in part responsible for the pulmonary artery hypertension, hypoxia, and increased inspiratory pressure that accompany early respiratory failure. Pulmonary platelet sequestration, an event often implicated in the pathogenesis of ARF,[1,3,4,5] occurred early in the course of ARF at a time that intracellular 5HT stores in circulating platelets were also low. This suggests that platelets were activated, entrapped in the lungs where they released 5HT. Since these platelet events occurred early in the course of ARF, it is plausible to expect that use of a 5HT receptor antagonist would have favorable effects only at this time. Our observations confirmed that the best results were noted early in ARF, that is, in the first day or two of intubation. Our initial considerations that 4 days may be used to separate early and late events in ARF were overly optimistic and need to be revised based on present data (Fig. 6).

Serotonin, when administered intravenously, causes an intense peripheral bronchospasm either by direct bronchoconstriction or indirectly by initiating a central neural

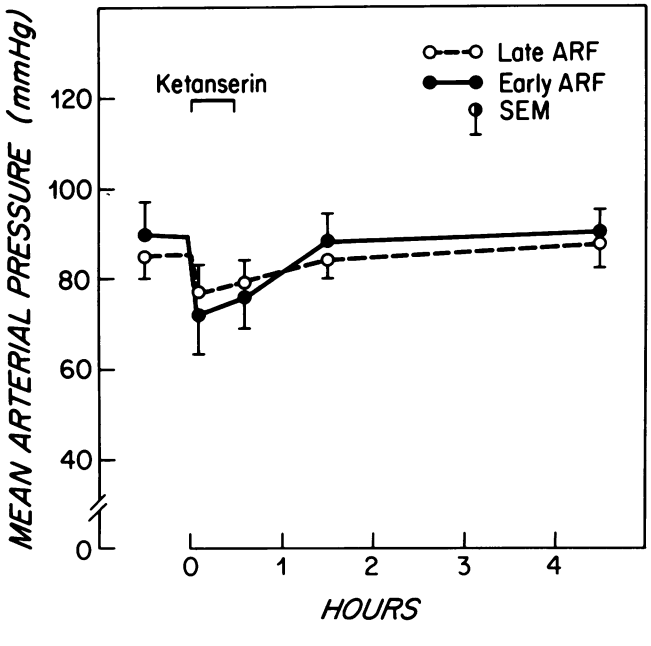


FIG. 1. Ketanserin led to a transient decline in mean arterial pressure in both groups of patients. This value returned to baseline within 1 hour following drug infusion.

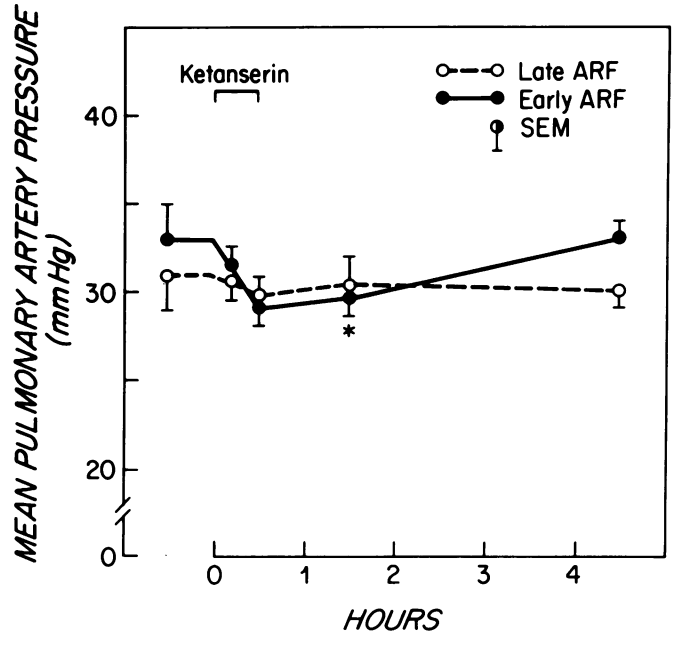
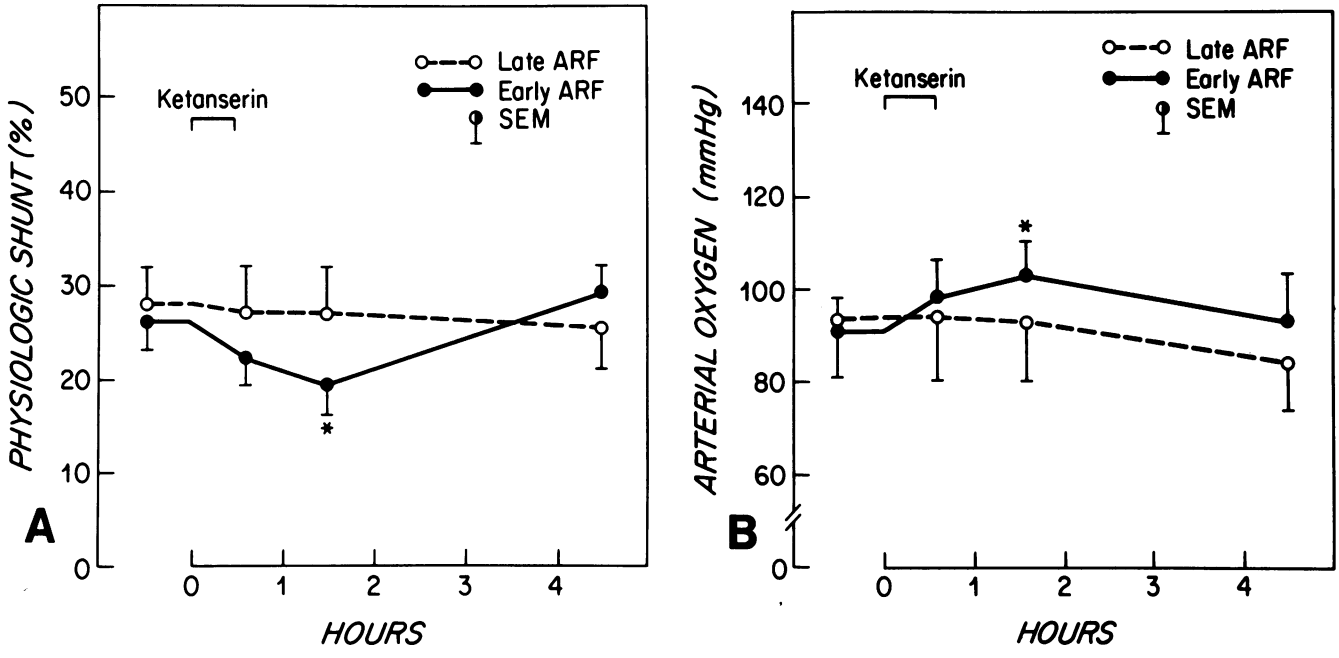


FIG. 2. Among patients given ketanserin early in the course of their acute respiratory failure (ARF), treatment resulted in a significant, reduction in mean pulmonary arterial pressure (MPAP). The serotonin antagonist had no effect on MPAP in patients with longer standing ARF.

reflex arc via the vagus.[14] The primary site of 5HT action is in airways less than 3 mm in diameter. Therefore, the functional effect is a reduction in compliance or rise in inspiratory pressure. Constriction of larger airways would be expected to lead to increased airways resistance. The bronchospasm induced by 5HT leads to hypoxemia and increases in $\dot{Q}_S/\dot{Q}_T$ because of continued perfusion of poorly or nonventilated alveoli (Fig. 3). This ability of 5HT to induce bronchoconstriction and severe hypoxia has been demonstrated following experimental pulmonary embolus, an event that can be completely reversed with ketanserin.[15]

An experimental infusion of 5HT will increase MPAP by directly constricting smooth muscle of both arterioles and postcapillary venules in the lung.[16] Blocking this smooth muscle effect of 5HT should in part reverse pulmonary hypertension. Ketanserin resulted in a 12% decline in MPAP in the early ARF group. Pulmonary artery hypertension is a consistent finding in ARF,[17] and, if severe, can precipitate right heart failure.

Ketanserin infusion was also associated with a prompt 11% decrease in MAP. The mechanism of this hypotensive response is disputed and may be unrelated to 5HT inhibition.[18,19] For example, results from animal studies suggest that ketanserin has an effect on the peripheral vasculature by inhibition of α-adrenergic receptors.[19] It might be argued that reducing the MAP would improve left ventricular function, reduce the PAWP, and thereby contribute to the observed fall in MPAP. Further, re-



FIGS. 3*A* and *B*. Patients in the early ARF group had a decline in physiologic shunt and rise in partial arterial oxygen pressure following ketanserin administration. These improvements were greatest 1.5 hours after the start of treatment.

duction in pulmonary hydrostatic pressures might reduce pulmonary edema as well as $\dot{Q}_S/\dot{Q}_T$. However, the lack of a temporal relationship between the changes in MAP and MPAP suggest that this mechanism of reduction in $\dot{Q}_S/\dot{Q}_T$, if any, was small. In addition, the decrease in MAP was not associated with significant changes in PAWP.

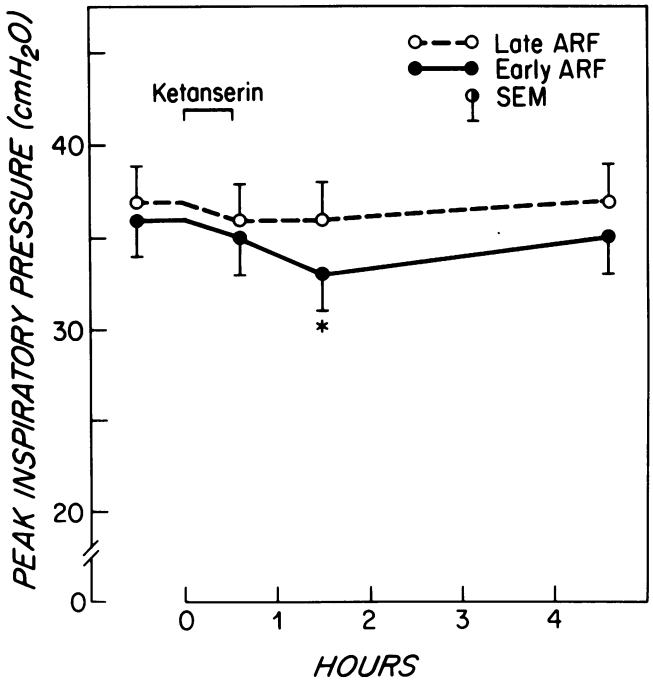


FIG. 4. The decrease in peak inspiratory pressure that occurred following infusion of ketanserin in the early acute respiratory failure (ARF) group indicates an improvement in lung compliance, presumably as a result of blocking 5HT-induced constriction of distal bronchioles. Reversing this peripheral airway constriction may explain, in part, the improvement in physiologic shunt.

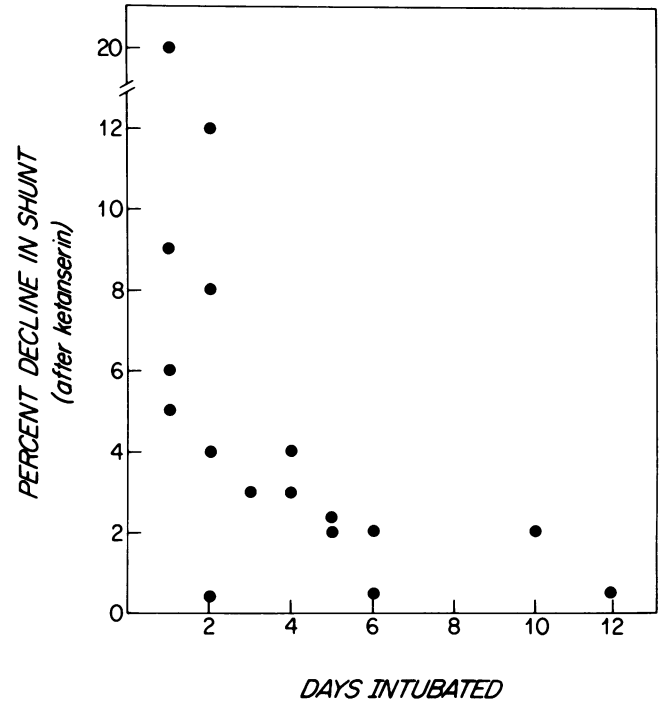
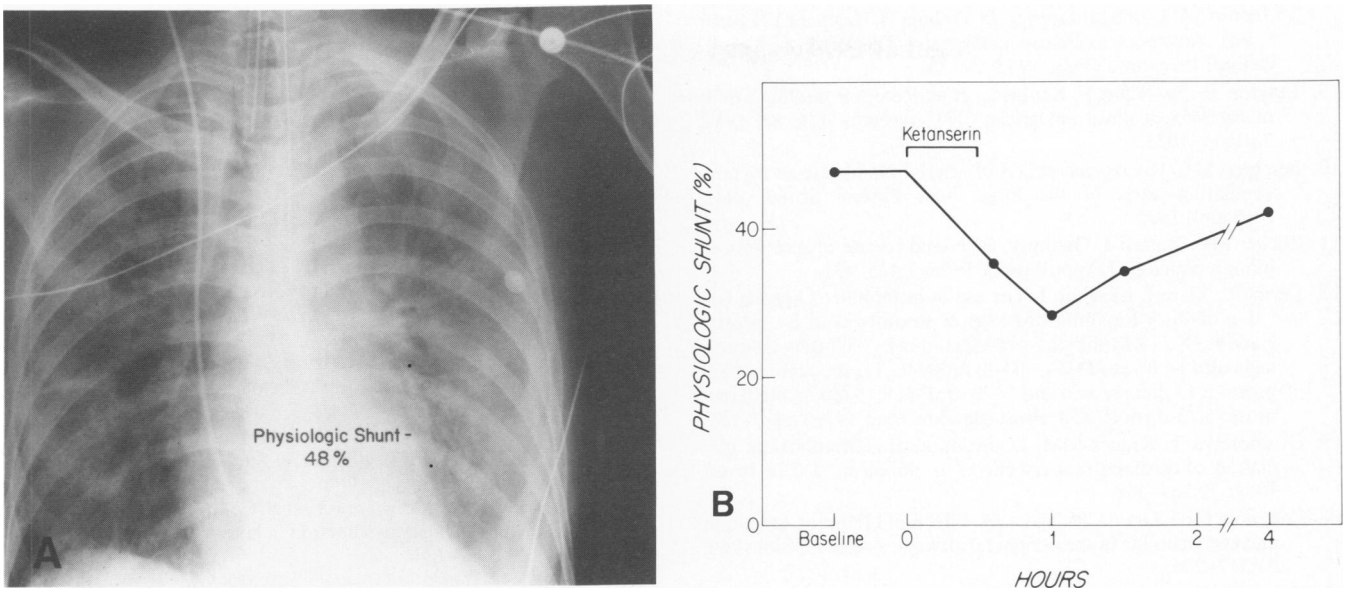


FIG. 5. Among patients from both groups, the decline in physiologic shunt following to ketanserin infusion was inversely related to the number of days of intubation.



FIGS. 6*A* and *B*. On the left is the portable chest x-ray of a patient with presumed mediastinitis taken 5 days after resection of an esophageal carcinoma. At the time of the x-ray the patient had a partial arterial oxygen pressure of 64 mmHg on an inspired oxygen fraction of 60%, with a physiologic shunt calculated as 48%. Treatment with ketanserin 2 hours after intubation led to a substantial fall in the physiologic shunt.

Agents that relax vascular smooth muscle such as nitroprusside, nitroglycerine, or isoproterenol, are capable of decreasing MPAP. Studies have demonstrated that treatment of ARF with these agents is often an effective means of modifying pulmonary artery hypertension.[20] However, in contrast to ketanserin, these agents may lead to a nonselective pulmonary vasodilatation, allowing perfusion of regions of the lungs that are poorly ventilated. This can worsen the shunt and exaggerate hypoxia.[20,21]

Sepsis is associated with a high incidence of ARF. Over 50% of patients who experience a hypotensive episode related to bacteremia will develop respiratory failure.[22] In the current study intra-abdominal sepsis was the etiology of ARF in 64% of patients. Not only platelets, but activated leukocytes are postulated to mediate the pulmonary dysfunction in sepsis.[1,2] Pulmonary leukocyte sequestration and subsequent activation with release of vasotoxic agents can cause endothelial cell damage and increased vascular permeability.[2,23] This is likely to have occurred in these study patients in view of the x-ray evidence of pulmonary edema combined with relatively low pulmonary vascular pressures (Tables 1, 2). Further, recent studies suggest that platelet-derived 5HT may enhance leukocyte adherence to endothelium and thereby the cytotoxicity of these cells.[24] However, it is doubtful that ketanserin's beneficial effect derives from its ability to modify leukocyte adherence, since reversal of the vasotoxic effects of these cells, such as pulmonary edema, is likely to take at least several hours to days.

Therapy late in the course of ARF was ineffective, but, even early therapy did not restore pulmonary function to normal. This suggests the importance of other factors such as intra-alveolar pulmonary edema as well as the activity of other vaso- and bronchoconstrictive agents. Examples of such agents are the oxygenation products of arachidonic acid. The leukotrienes and TxA_2 are potent spasminogens. They can be produced by circulating cells as well as the lungs themselves. The fact that plasma TxB_2 levels were somewhat elevated suggests that this prostanoid may be exerting a significant pulmonary vaso- and bronchospastic effect.

In summary, these data indicate that 5HT inhibition may favorably influence ARF secondary to a variety of causes. The results are favorable when therapy is delivered within the first 1 to 2 days of intubation.

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